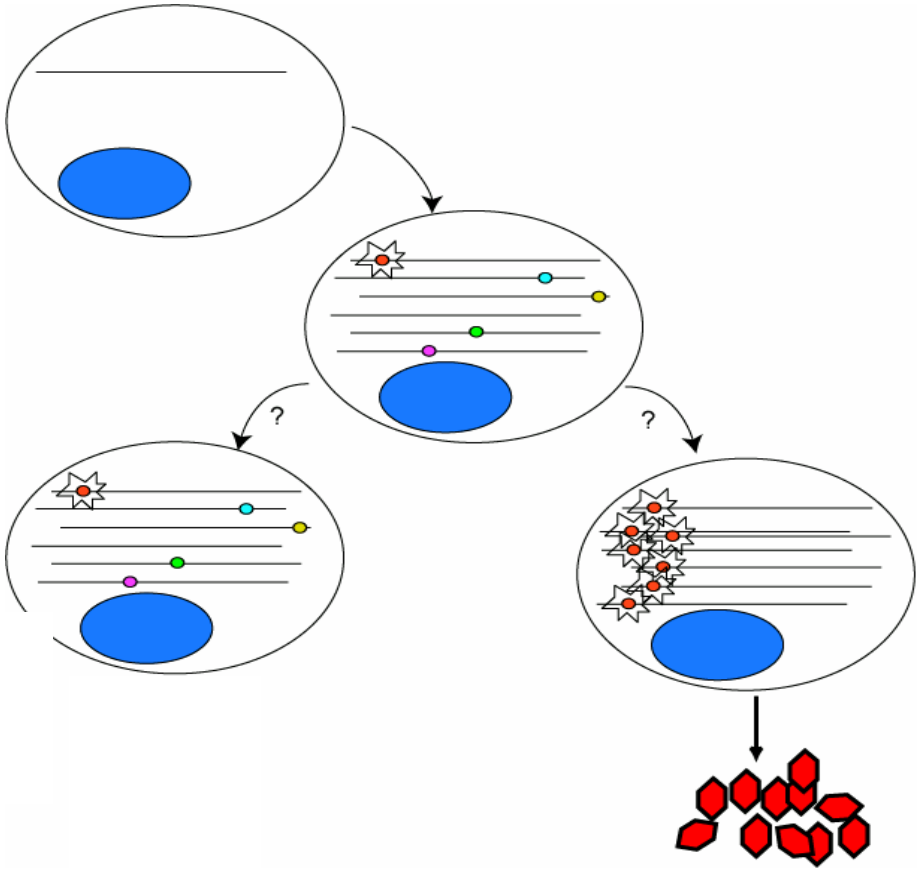
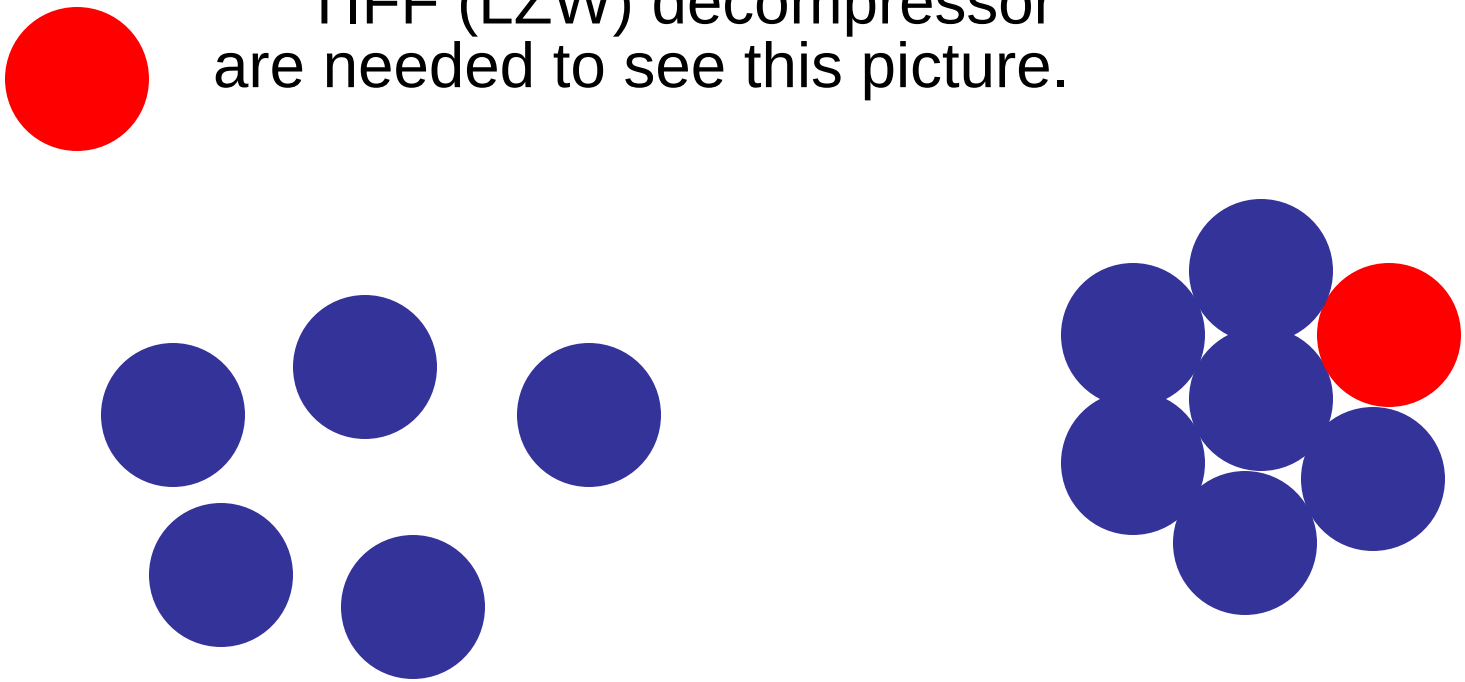
What affects whether or not a drug-resistant virus escapes the cell in which it arose?



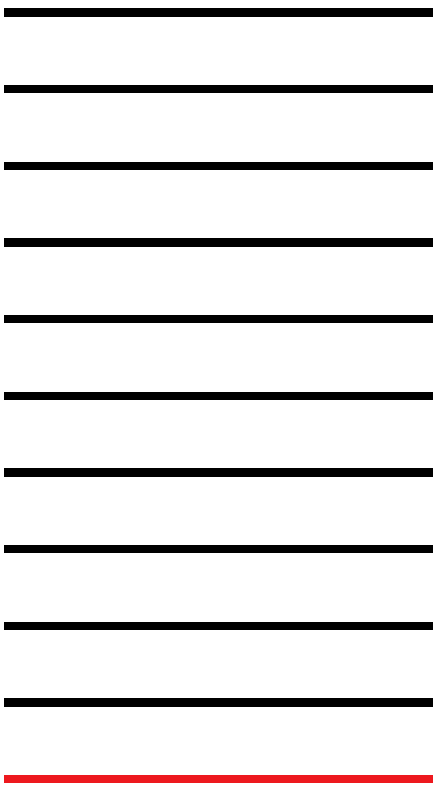
If proteins from different viruses in the same cell cooperate, drug resistant viruses will be inhibited

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.



Proof of concept: are pleconaril (WIN)-sensitive viruses dominant?

Drug-sensitive and drug-resistant genomes at 10:1 ratio in doubly infected cells



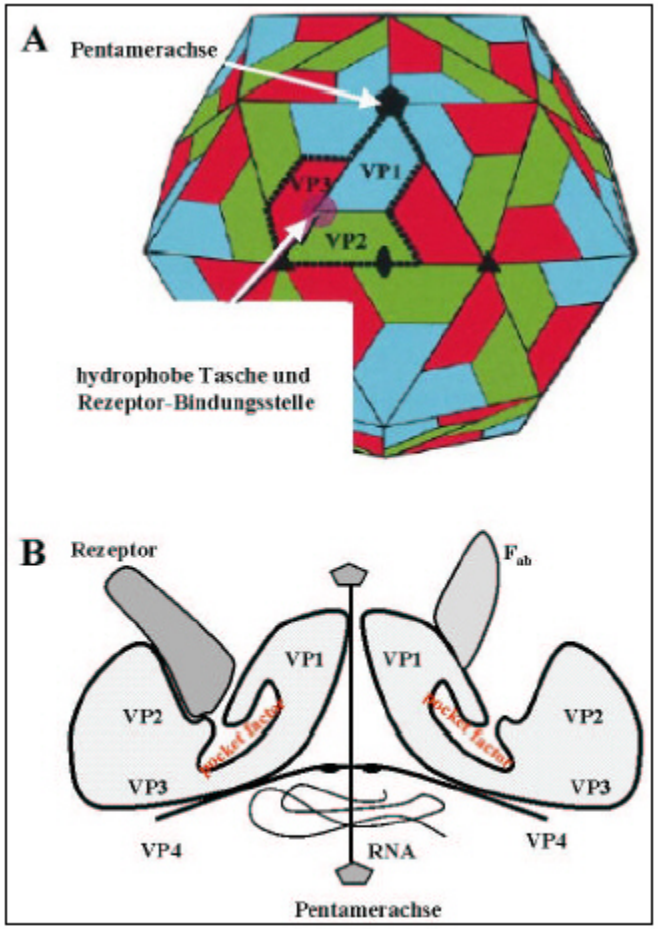
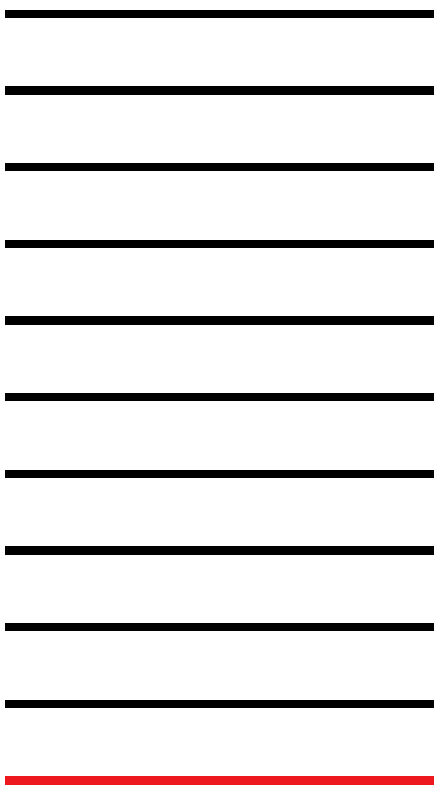
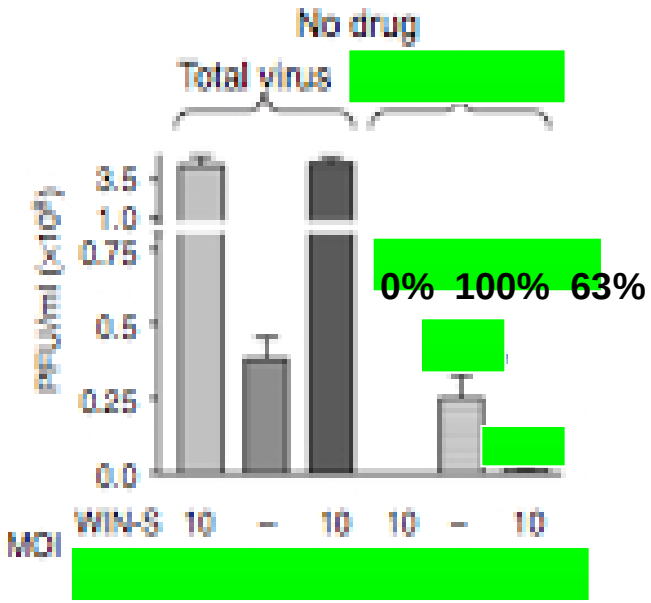


Abb. 1: Kapsidstruktur von Rhino- und Enteroviren (1A) und Modell zur Rezeptorbindung (1B) modifiziert nach Rossmann

Dominance of pleconaril (WIN)-sensitive viruses

Drug-sensitive and drug-resistant genomes at 10:1 ratio in doubly infected cells

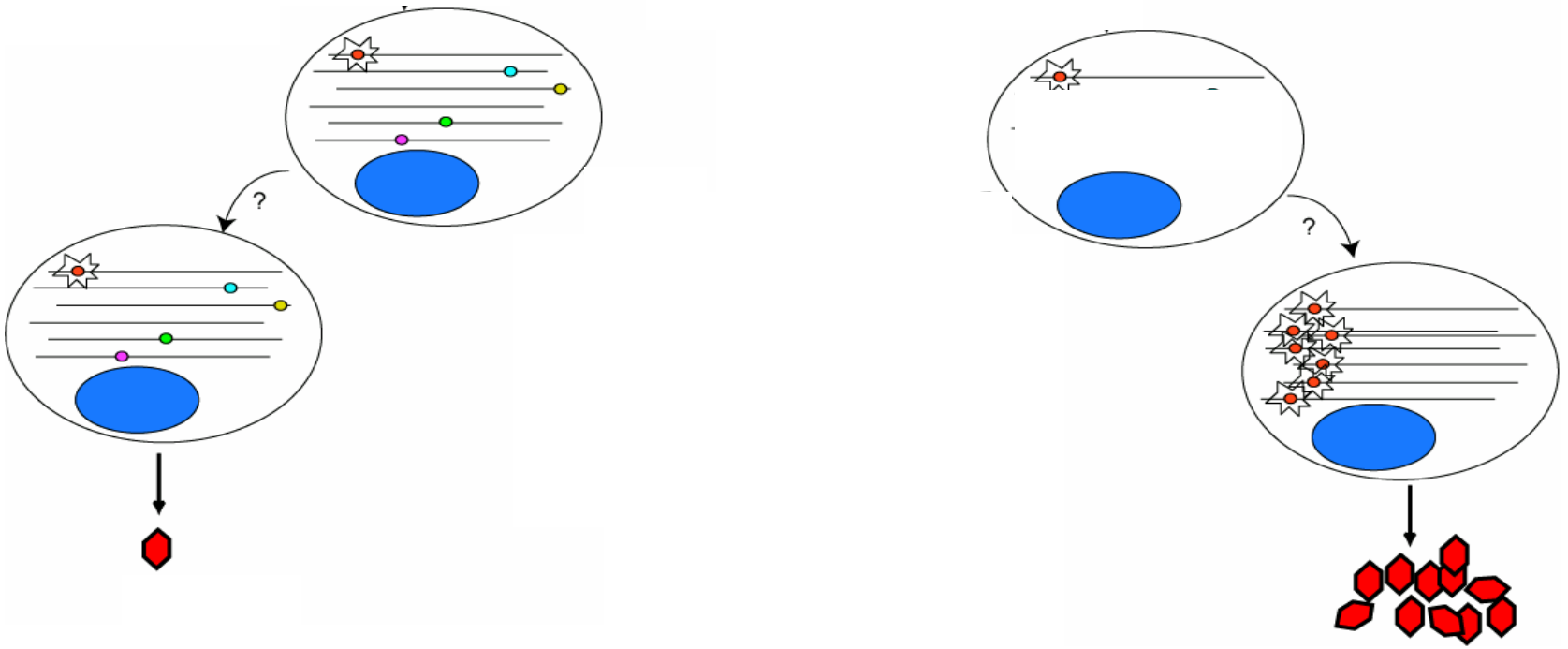




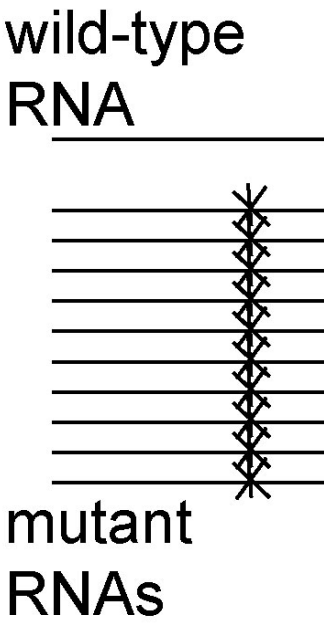
RNA

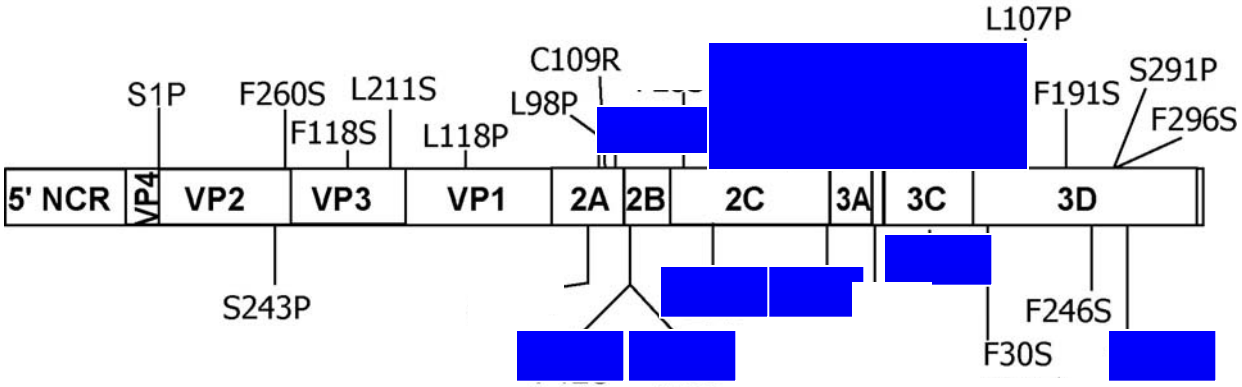
Virus

WIN-sensitive genomes can dominantly inhibit the outgrowth of drug-resistant genomes



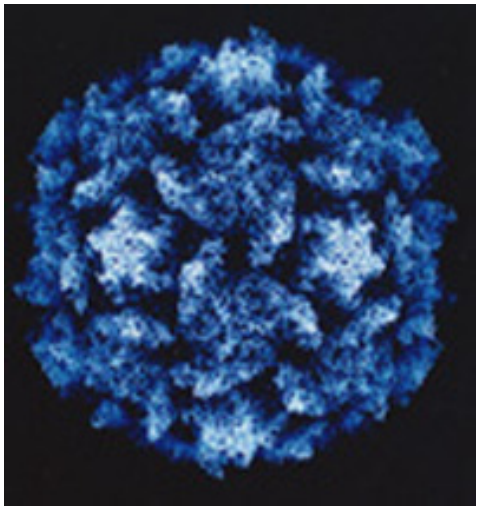
Lethal mutations in poliovirus genomes: Co-transfection with wild-type poliovirus RNA at 10:1 ratio reveals many [redacted] mutations*

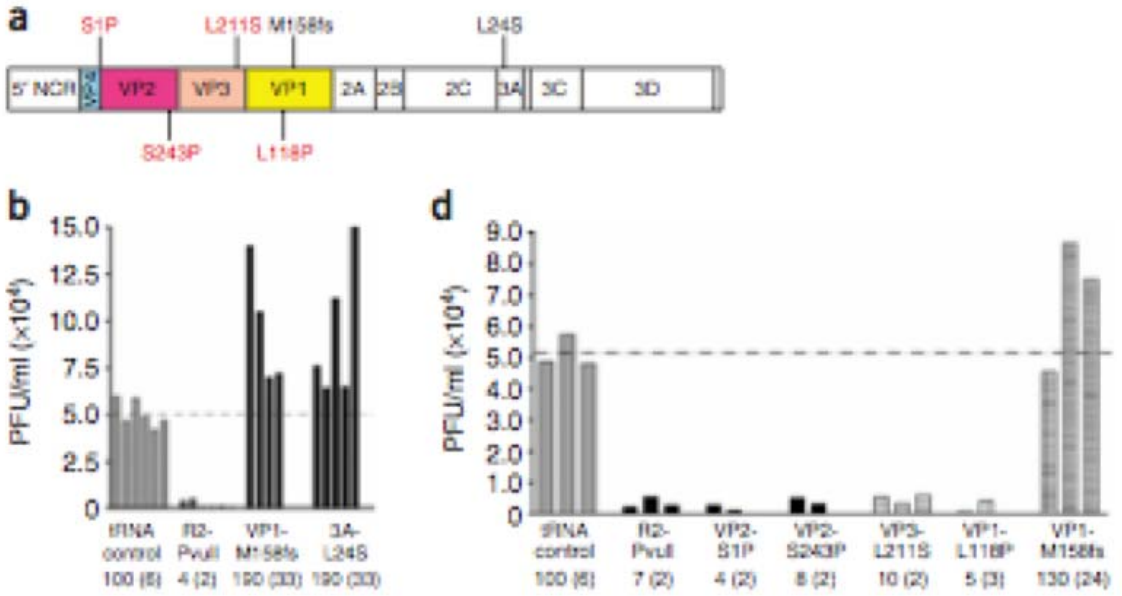




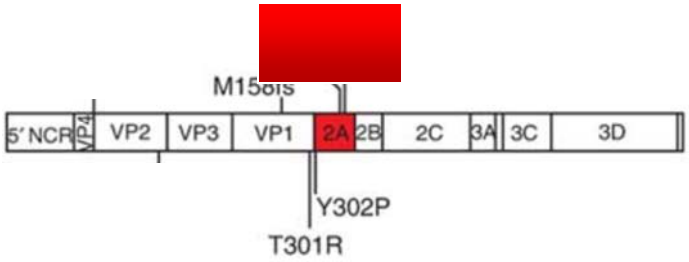
*less than 5-fold inhibition of wild-type growth

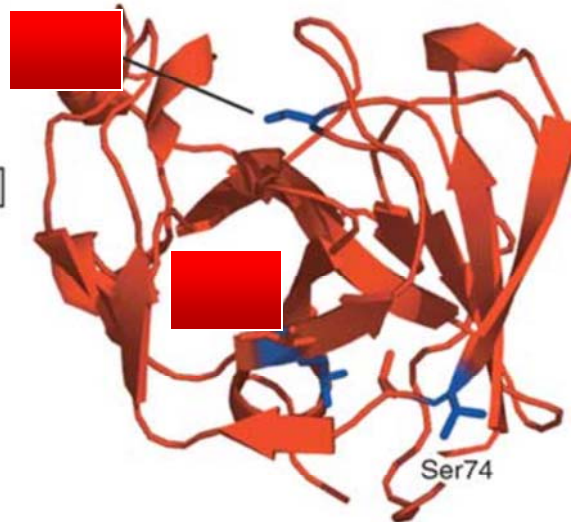
All tested point mutations in capsid proteins are dominant

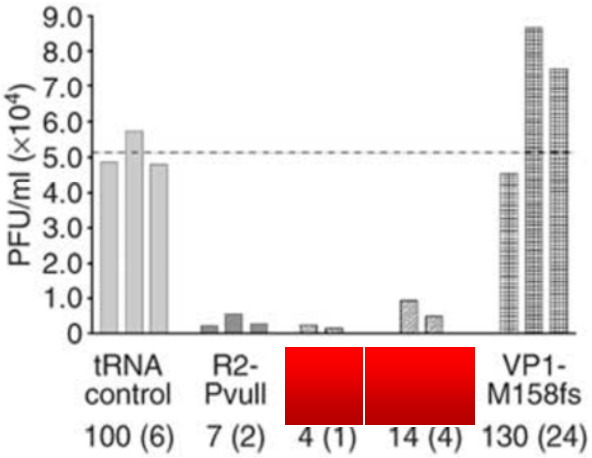




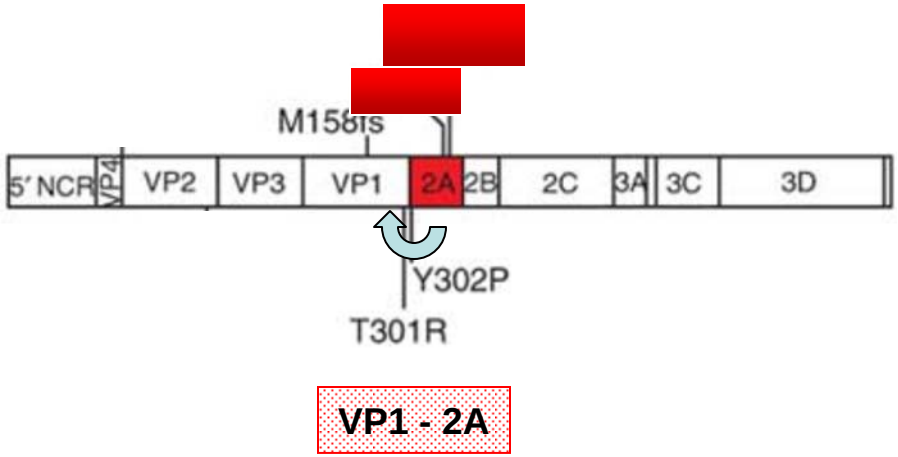
Mutations in 2A protease, the “minor protease” of poliovirus are dominant





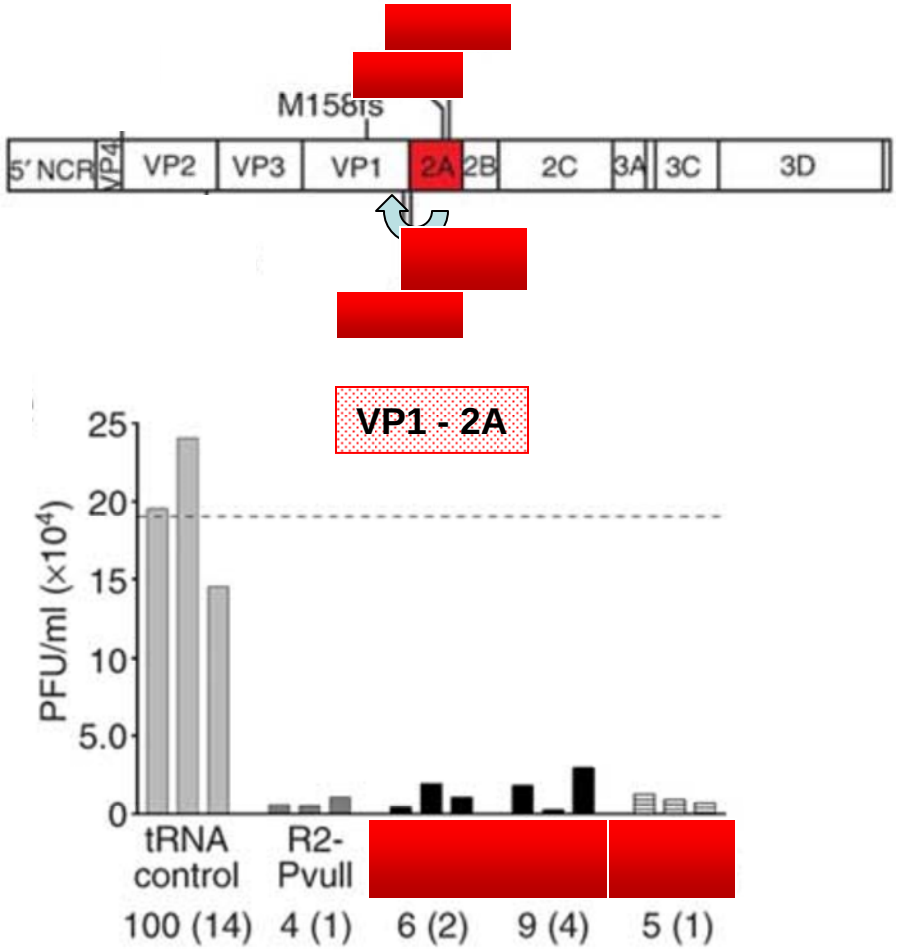


Is the uncleaved precursor (VP1-2A) inhibitory to virus growth?

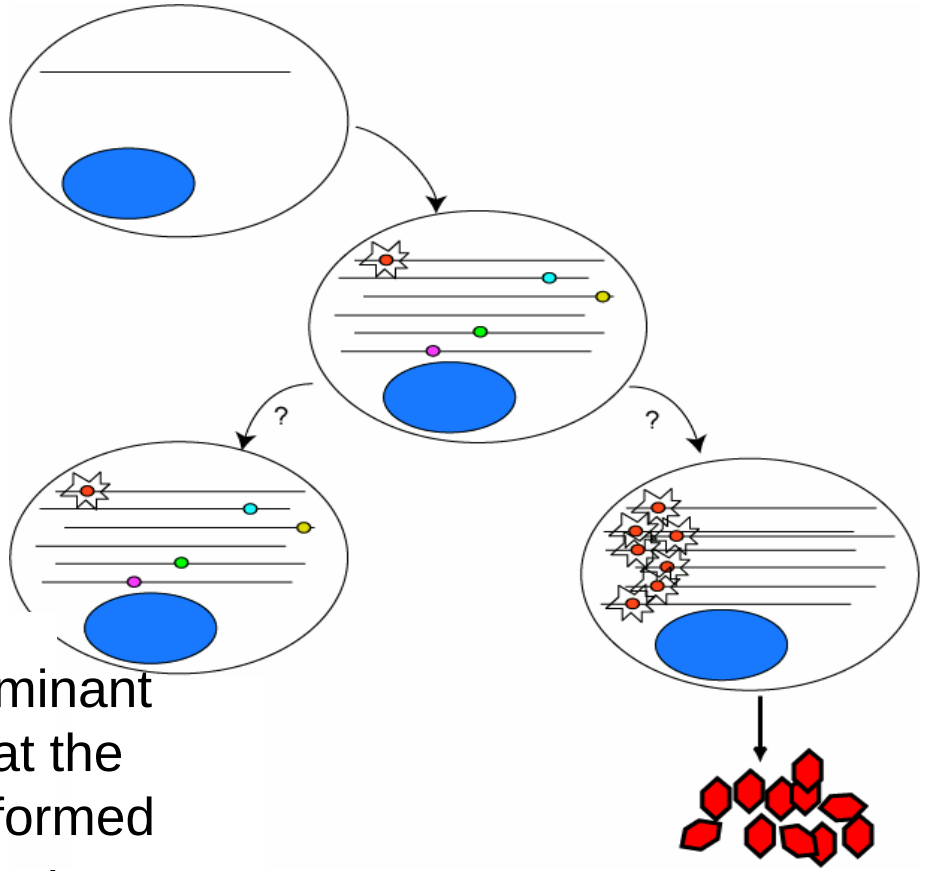


[redacted]

Mutations in the VP1/2A cleavage site are also dominant. Dominance of 2A protease mutants likely results from toxicity of precursor!

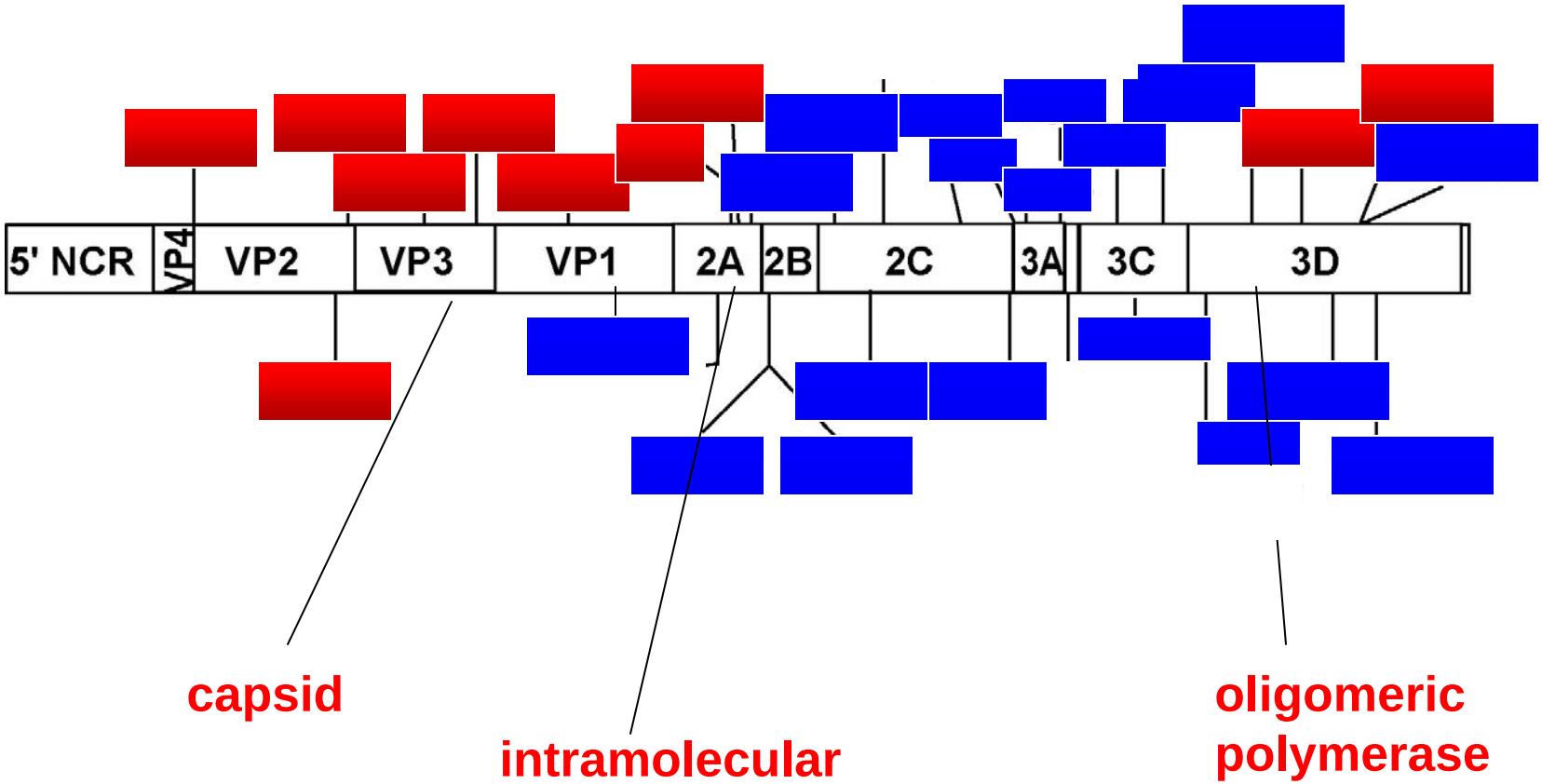


How to discourage selection for drug resistence?



Choose a dominant drug target at the beginning, informed by viral genetics

Postulated dominant drug targets in positive-strand RNA viruses based on poliovirus homologs



Most common HCV drug targets:
Polymerase active site
major protease NS3/4
NS3 helicase (2C homolog)

Dominant alleles in **cores** and **capsids, oligomeric polymerases** and **exclusively intramolecularly cleaving proteases** of RNA viruses can guide the design of antivirals to these potentially **'dominant drug targets'**

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